Undetectable Plasma Creatinine in a Paralyzed Patient Infected With Human Immunodeficiency Virus

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Questions:
1. What are this patient's most striking laboratory findings?
2. How do you explain these findings?
3. What is the most common method of measurement of serum/plasma creatinine concentration?
4. What are common interferents in this method?
5. How would you determine whether or not a patient's serum/plasma contains an interfering substance(s) in the method used most commonly to quantify creatinine concentration?
6. What is the most likely explanation for this patient's extremely low and undetectable creatinine levels?
7. What difficulties are presented to the clinician in assessing this patient's renal function?
8. What other test(s) might have proved helpful in this assessment?

Possible Answers:
1. Markedly decreased CD4 count, very low CD4/CD8 ratio (Table 1); and, persistently low creatinine values during hospital days 54 to 100, including an undetectable creatinine on days 62 and 63 (Figure 1).

2. The markedly decreased CD4 count is consistent with the patient's HIV status, high viral load, and very low CD4/CD8 ratio. The finding of undetectable plasma creatinine levels on days 62 and 63 of hospitalization (Figure 1) prompted additional laboratory studies to ascertain whether or not the patient's plasma contained any substance(s) that may have interfered in the assay used to measure the patient's creatinine concentration.

3. The Jaffe reaction (or modification of) is the most commonly used method of measuring serum/plasma and urine creatinine concentration. The Jaffe reaction for creatinine determination is based on the formation of a yellow-orange chromogen when picric acid in alkaline solution is added to serum, plasma, or urine:

\[
\text{Creatinine} + \text{picric acid} \xrightarrow{\text{alkaline solution}} \text{creatinine-picric acid complex}
\]

4. The Jaffe method is affected by numerous interferents that can cause creatinine results by this method to be falsely increased or decreased. Examples of interferents include glucose, protein, bilirubin, hemolysis, and lipemia.1 Modifications to the original Jaffe method and the advent of kinetic enzymatic methods, with and without rate blanking, have reduced the error in creatinine measurement caused by the presence of various interferents.

5. By testing the patient's serum/plasma suspected of containing a substance(s) that interfered in the creatinine assay based on the Jaffe reaction using a creatinine assay based on a different methodology and by performing mixing studies of the patient's serum/plasma with serum/plasma, containing a high

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**Patient**


**History of Present Illness**

The police found him lying naked in a ditch, the victim of an apparent assault. He had multiple signs of trauma, including numerous bruises and abrasions on his face and extremities. He was conscious but was confused and combative.

**Physical Examination**

The patient's vital signs were: temperature, 96.8°F; pulse, 72 beats/min; respirations, 20 breaths/min; blood pressure, 131/88 mmHg. His oxygen saturation on room air was 96%. He could follow verbal commands but could not communicate. He showed bilateral injected sclera, left periorbital swelling, and bilateral round and reactive pupils. He had a swollen upper lip and limitation in his ability to open his mouth. There was no evidence of any other abnormalities. He was admitted to the hospital for further evaluation.

**Past Medical History**

Seven years ago, he was diagnosed with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). In addition, he had been treated for Pneumocystis carinii (PCP) pneumonia 4 months prior to this current hospitalization during which time his HIV viral load was 330,000 copies.

**Principal Laboratory Findings**

Table 1 and Figure 1

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1. Markedly decreased CD4 count, very low CD4/CD8 ratio (Table 1); and, persistently low creatinine values during hospital days 54 to 100, including an undetectable creatinine on days 62 and 63 (Figure 1).

2. The markedly decreased CD4 count is consistent with the patient's HIV status, high viral load, and very low CD4/CD8 ratio. The finding of undetectable plasma creatinine levels on days 62 and 63 of hospitalization (Figure 1) prompted additional laboratory studies to ascertain whether or not the patient's plasma contained any substance(s) that may have interfered in the assay used to measure the patient's creatinine concentration.

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4. The Jaffe method is affected by numerous interferents that can cause creatinine results by this method to be falsely increased or decreased. Examples of interferents include glucose, protein, bilirubin, hemolysis, and lipemia.1 Modifications to the original Jaffe method and the advent of kinetic enzymatic methods, with and without rate blanking, have reduced the error in creatinine measurement caused by the presence of various interferents.

5. By testing the patient's serum/plasma suspected of containing a substance(s) that interfered in the creatinine assay based on the Jaffe reaction using a creatinine assay based on a different methodology and by performing mixing studies of the patient's serum/plasma with serum/plasma, containing a high
creatinine concentration, obtained from another patient. We mixed the patient’s plasma with an equal volume of plasma from a patient with chronic renal failure whose plasma creatinine concentration was 3.3 mg/dL. Subsequently, the mixture was tested by two different creatinine methods: 1 based on the Jaffe reaction and another based on a coupled-enzyme method—both used according to the manufacturer’s instructions. According to the manufacturer’s product inserts, the enzymatic method is more specific for creatinine and less subject to analytical interferences, particularly bilirubin, than the method based on the Jaffe reaction. The enzymatic method uses a coupled-enzyme reaction with formation of a quinoneimine chromogen that is measured spectrophotometrically. The creatinine values obtained by both creatinine methods in the sample mixture, after correcting for the dilution and the creatinine contributed by each sample used to prepare this mixture, were in excellent agreement with the dilution and the creatinine contributed by each sample used.

For more than 40 years, serum or plasma creatinine concentration has been the most commonly used serum/plasma marker of renal function. However, serum/plasma creatinine measurements are affected by a number of factors not related to renal function, particularly age, gender, and muscle mass. In the patient presented in this case study, the rapid decline in his muscle mass rendered his serum/plasma creatinine level essentially useless for monitoring renal function.

Sarcopenia. Thus, the effect of HIV infection in a patient who is paralyzed is likely to augment, or at least be additive to, the effect of paralysis on muscle wasting.

Alternatives for the assessment of renal function or glomerular filtration rate (GFR) in the patient include measurement of the clearance of exogenously administered substances (eg, inulin, iohexol, or $^{51}$Cr-EDTA), which do not require the measurement of plasma creatinine, or the measurement of serum/plasma cystatin C. Cystatin C, a small 122-amino acid-containing protein, is a cysteine protease inhibitor expressed in all nucleated cells. Cystatin C is produced at a constant rate and is freely filtered by the glomerulus. It is reabsorbed by the tubular epithelial cells and subsequently catabolized. Additionally, it is not affected by muscle mass, gender, or age as is creatinine. Because of these features, the plasma concentration of cystatin C can be used as a reliable measure of the GFR. It has been suggested that serum/plasma cystatin C is an ideal endogenous marker for assessing renal function.

Patient’s Clinical Course and Outcome: The patient had multiple neurological problems during his hospital stay, despite an initial electroencephalogram (EEG) which did not show any epileptiform activity. Moreover, multiple testing of cerebrospinal fluid at various stages of his hospitalization did not reveal the etiology of his neurological problems. He received multiple courses of antibiotics, but ultimately it was felt that he had traumatic meningitis and not infectious meningitis. During his hospital stay, he developed status epilepticus and required intubation, mechanical ventilation, and treatment with phenytoin and valproic acid. His seizures were ultimately controlled.
and he was weaned off the phenytoin and kept on a maintenance regimen of valproic acid. Multiple radiologic scans of his brain and spine revealed subarachnoid hemorrhage and some dilated ventricles consistent with hydrocephalus. On hospital day 8, he developed flaccid paralysis of the lower extremities. Extensive work-up failed to reveal the exact etiology of the paralysis, and it was felt that it was a myelitis related to his HIV infection or another, unidentified virus. In addition to the medications mentioned above, he was treated with azithromycin and trimethoprim/sulfamethoxazole to prevent opportunistic infections and with famotidine to prevent gastrointestinal ulcers. He was not treated with antiretroviral agents while he was an inpatient. The patient ultimately lapsed into a vegetative state attributed to his traumatic brain injury. He was not able to follow commands or communicate, and he never regained any strength in his lower extremities.

**Keywords**
creatinine, human immunodeficiency virus, Jaffe reaction, cystatin C, renal function